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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/811,870 | 03/21/2001 | Philip A. Cole | 01107.00108 | 8634 |

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| STEADMAN, DAVID J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | |

DATE MAILED: 11/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/811,870 | COLE ET AL. | |
| | Examiner | Art Unit | |
| | David J Steadman | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-68* is/are pending in the application.

4a) Of the above claim(s) *16-57,59,61,62,64,65 and 68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,58,60,63,66 and 67* is/are rejected.

7)☒ Claim(s) *15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Status of the Application*

**[1]** Claims 1-68 are pending.

**[2]** Applicant's election of Group I, claims 1-15, 58, 60, 63, 66, and 67 in the amendment filed August 22, 2003, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

**[3]** Claims 16-57, 59, 61-62, 64-65, and 68 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the amendment filed August 22, 2003.

**[4]** Receipt of a sequence listing in computer readable form and paper copy filed August 22, 2003, is acknowledged.

**[5]** Claims 1-15, 58, 60, 63, 66, and 67 are being examined only to the extent the claims read on the elected invention.

### *Priority*

**[6]** Applicants' claim to domestic priority under 35 USC § 119(e) to provisional application 60/190,799, filed March 21, 2003, is acknowledged.

### *Claim Rejections - 35 USC § 112, Second Paragraph*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

**[7]** Claim 66 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 66 recites "wherein a nitrogen atom replaces a hydroxyl oxygen on the tyrosine". However, it is noted that neither claim 60 nor 63 (from which claim 66 is dependent upon) recites the limitation of "a tyrosine" in regards to an amino acid. While claim 63 recites "tyrosine protein kinase", this limitation merely limits the protein kinase to a tyrosine protein kinase and does not refer to an amino acid. As such, there is no antecedent basis for the term "the tyrosine" as recited in claim 66.

### *Claim Rejections - 35 USC § 112, First Paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

**[8]** Claims 1-14, 58, 60, 63, 66, and 67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a genus of bisubstrate inhibitors of any protein kinase or an insulin receptor kinase. For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the genus of claimed bisubstrate inhibitors, i.e., compound 2 (see Figure 1). The specification fails to describe any additional representative species of the claimed genus of bisubstrate inhibitors. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". Regarding the claimed genus of bisubstrate inhibitors of insulin receptor kinase, it is noted that while the genus is functionally limited to those species with insulin receptor kinase inhibitory activity, the

claimed genus encompasses species having widely variant structures with respect to the tether and peptide moiety. Moreover, regarding the claimed genus of bisubstrate inhibitors of any protein kinase, it is noted that the claimed genus encompasses species having widely variant structures with respect to the tether and peptide moiety AND widely variant functions with respect to their ability to inhibit a vast array of protein kinases. As such, the disclosure of the structure of the single representative species of compound 2 is insufficient to be representative of the attributes and features of all species encompassed by the recited genus. Given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

**[9]** Claims 1-14, 58, 60, 63, 66, and 67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compound 2 as set forth in Figure 1, does not reasonably provide enablement for *all* bisubstrate inhibitors of insulin receptor kinase or any protein kinase as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir.

1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: The claims are so broad as to include *all* bisubstrate inhibitors of insulin receptor kinase or any protein kinase as encompassed by the claims. The broad scope of the claimed bisubstrate inhibitors is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of inhibitors broadly encompassed by the claims. In this case the disclosure is limited to compound 2 as set forth in Figure 1.

- The lack of guidance and working examples: The specification provides only a single working example of the claimed inhibitor, i.e., compound 2. This single working example fails to provide the necessary guidance for making and using the entire scope of claimed inhibitors, particularly in the design of the peptide moiety structure. In this case, the claims encompass peptide moieties that are essentially unlimited in composition and number or amino acids and the specification fails to provide guidance regarding those amino acids that are required for inhibition of an insulin receptor kinase or any protein kinase as encompassed by the claims. The ability of an inhibitor to inhibit the function of an enzyme is largely dependent upon the structure of the inhibitor. In this

case, the specification fails to provide the necessary guidance for determining the structures of those peptide moieties that can be successfully applied for inhibition of an insulin receptor kinase or any protein kinase.

- The high degree of unpredictability in the art: The structure of an enzyme inhibitor determines its specificity and efficacy. For example, Parang et al. (*Nat Struc Biol* 8:37-41; cited in the IDS filed June 28, 2001) teach, "the peptide moiety is an essential contributor to the inhibitory potency of compound 2" in the inhibition of insulin receptor kinase (page 39, left column, top). Thus, one of skill in the art would recognize that alterations in the peptide moiety can significantly alter the efficacy of a bisubstrate inhibitor. Predictability of which changes can be tolerated in an inhibitor's structure and obtain the desired biological activity requires a knowledge of and guidance with regard to which amino acids in the peptide moiety, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the inhibitor's peptide moiety structure relates to its function. The positions within the peptide moiety of compound 2 where modifications, *e.g.,* insertions, deletions, and substitutions, can be made with a reasonable expectation of success in obtaining an inhibitor having the desired activity/utility are limited in any inhibitor and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification to diminish with each further and additional modification to the peptide moiety. In this case, the necessary guidance has not been provided in the specification as explained in detail above. Thus, a skilled artisan would recognize the high degree of unpredictability in modifying the peptide moiety of

compound 2 with an expectation of obtaining an inhibitor having the desired activity. Furthermore, there is a high degree of unpredictability that an effective inhibitor of a specific kinase, e.g., insulin receptor kinase, will also have effective inhibitory activity against other protein kinases. For example, Miller (*Nat Struc Biol* 8:16-18; cited in the IDS filed June 28, 2001) teaches, "[w]hile the design by Parang et al. appears successful, it is difficult to predict how selective such inhibitors will be for closely related tyrosine kinases" (page 17, middle column, bottom). Also, Parang et al. teach that compound 2 was not an effective inhibitor of another kinase – Csk, a protein tyrosine kinase (page 39, left column, top). The specification fails to provide the necessary guidance that would enable a skilled artisan to correlate the inhibitory activity of a specific kinase inhibitor to other kinases and, consequently, a skilled artisan would recognize the unpredictability that the inhibitory activity of a kinase inhibitor would be broadly applicable to any protein kinase.

- The amount of experimentation required is undue: While methods of screening kinase inhibitors are known in the art, it is not routine in the art to screen for *all* bisubstrate inhibitors of any protein kinase or an insulin receptor kinase as broadly encompassed by the instant claims. In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

## ***Conclusion***

**[10]** Status of the claims:

- Claims 1-68 are pending.
- Claims 16-57, 59, 61-62, 64-65, and 68 are withdrawn from further consideration as being drawn to a nonelected invention.
- Claims 1-14, 58, 60, 63, 66, and 67 are rejected.
- Claim 15 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. Any

inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652

11-14-03
DAVID STEADMAN
PATENT EXAMINER